American Society of Hematology
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August 27, 2026

On behalf of the American Society of Hematology (ASH), we are writing in response to the National Coverage Analysis (NCA) for Autologous Stem Cell Transplantation (AuSCT) for Multiple Myeloma (MM), proposed by the Centers for Medicare & Medicaid Services (CMS) on July 29, 2026. ASH appreciates CMS's attention to this specific aspect of the National Coverage Determination (NCD). We want to extend our thanks to the Agency for responding to our request for reconsideration by proposing to expand coverage for AuSCT for MM patients when the International Staging System (ISS) or its revisions are used in the patient's risk assessment.

As CMS noted, the Durie Salmon Staging System (DSSS) is no longer widely used and has largely been supplanted by more accurate staging systems. At the time the NCD was initially published in 2000, DSSS was the most common prognostic standard in MM. Although useful to assess for tumor burden and prognosis, DSSS predated the modern distinction between smoldering (an asymptomatic precursor condition) and active multiple myeloma (Ghobrial et al., *Blood* 2014, PMID: 25298034; Durie and Salmon, *Cancer* 1975, PMID: 1182674; Kyle and Greipp, *N Engl J Med* 1980, PMID: 7374679; International Myeloma Working Group, *British Journal of Haematology* 2003, PMID: 12780789). Given that DSSS Stage I included a heterogeneous population that could include patients with asymptomatic disease, these patients were generally excluded from the pivotal trials establishing upfront AuSCT as a standard of care for the treatment of MM. The corresponding Medicare coverage restriction was therefore appropriate at the time because many DSSS Stage I patients would not have required treatment, including AuSCT.

Since the development of the original NCD, the diagnosis, risk stratification, and treatment of MM have evolved substantially, and more accurate prognostic tools have become available to assess disease risk. Importantly, while prognostic tools may help estimate prognosis and clinical outcomes, and may support physician-patient discussions about the disease and care planning, transplant eligibility is not determined by prognostic stage but instead by clinical appropriateness, centered on active myeloma requiring therapy, and patient fitness.

In the evidentiary review, CMS analyzed several risk assessment models for MM patients undergoing AuSCT, as summarized in Table 2. As noted in the proposed decision memo, ISS and its revisions are widely used across institutions and health care systems as prognostic tools. Based on these updates in the field and in consideration of how the NCD is structured, ASH supports including ISS and its revisions in the NCD language.

The ISS tool was developed and validated in patients with active myeloma requiring treatment (unlike DSSS). Patients across ISS Stages- Stage I, II, or III- have been included in contemporary clinical trials for transplantation (Greipp et al., *J Clin Oncol* 2005, PMID: 15809451; Palumbo et al., *J Clin Oncol* 2015, PMID: 26240224). In fact, CIBMTR data show that providing AuSCT across ISS Stages is routinely

2021 L Street, NW, Suite 900, Washington, DC 20036-4929 ph 202.776.0544 fax 202.776.0545 e-mail ASH@hematology.org

and successfully performed among patients who are over 65 and suitable for transplant; transplant provides a valuable and life-altering treatment option (Munshi et al., *Cancer* 2020, PMID: 32965680). The ISS staging system is commonly used for risk stratification and subgroup analyses in clinical trials and to understand differences in outcomes according to baseline prognostic risk. The following clinical trials collectively support PFS benefit across ISS stages, including Stage I:

- In 2009, the IFM study aimed to understand the role and timing of transplantation in MM treatment using PFS as the primary endpoint. This study showed improved PFS with upfront AuSCT across ISS Stages, including in the prespecified ISS Stage I subgroup. (Attal et al., *N Engl J Med* 2017. PMID: 28379796)
- The IFM trial findings were later confirmed by the 2022 DETERMINATION clinical trial, a modern U.S. randomized trial aimed to understand adding AuSCT to a common treatment regimen for newly diagnosed MM patients, using PFS as the primary outcome. Evidence from the study demonstrated significant PFS benefit with upfront AuSCT for patients with active multiple myeloma, supporting the benefit of upfront AuSCT for patients across ISS stages, including in patients with Stage I ISS (HR 1.83, 95% confidence interval 1.32-2.54, favoring RVd+AuSCT; Figure S3, Supplementary Materials). (Richardson et al., *N Engl J Med* 2022. PMID: 35660812)
- In 2020, the EMN02/HO95 aimed to understand the role of AuSCT in comparison to novel agents among patients with newly diagnosed MM. This trial found improved PFS with AuSCT versus non-transplant modalities. Patients were enrolled across ISS Stages I-III, and the PFS benefit of high-dose melphalan/AuSCT was retained in the prespecified ISS stage I subgroup (HR 0.69, 95% CI 0.48-0.98; P=0.037). (Cavo et al., *Lancet Haematol* 2020. PMID: 32359506.)
- Lastly, the FORTE trial evaluated multiple treatment strategies with and without AuSCT in transplant-eligible patients with newly diagnosed MM. The study demonstrated improved PFS with KRD plus AuSCT versus 12 cycles of KRD (HR 0.61). Importantly, patients across ISS stages were prospectively enrolled, and randomization was stratified by ISS stage (I vs. II/III), reflecting the routine inclusion of patients across ISS groups in contemporary transplantation trials. Approximately half of the study population had ISS stage I disease. (Gay et al., *Lancet Oncol* 2021. PMID: 34774221.)

Based on this evidence proving benefit of AuSCT across ISS Stages, ASH recommends CMS consider coverage for all ISS Stages, expanding from only ISS Stages II and III to also to include ISS Stage I. ASH recommends the following updated language. CMS proposed language is in red font, and our recommendation is indicated in green font.

> Effective October 1, 2000, single AuSCT is ~~only~~ covered for Stage II or III patients using Durie Salmon or International Staging System and its revisions that fit the following requirements.

Instead, we propose:

> Effective October 1, 2000, single AuSCT is ~~only~~ covered for Stage II or III patients using Durie Salmon or any Stage using the International Staging System and its revisions that fit the following requirements.

ASH believes this update will better align the NCD with modern myeloma practice, for which transplant candidacy is appropriate across ISS stages, and for which eligibility is then determined by clinical appropriateness. ASH recommends this clarification to ensure that patients with MM, and for whom AuSCT would be medically necessary, have appropriate coverage.

This revision would also support the longevity and clinical relevance of this policy; as prognostic tools and the clinical evidence to support standard of care continues to evolve, it would be beneficial for Medicare coverage policy to ensure access and avoid unintentional limitations based on stage alone. For example, the R2-ISS model (a revision of ISS staging) includes Stage IV disease, underscoring the need for clear, durable, and clinically aligned language to avoid reinforcement of restricting AuSCT coverage to Stages II and III (D'Agostino et al., *J Clin Oncol*, 2022, PMID: 35605179). Expanding the language to include all ISS Stages would support inclusion of the appropriate population and ongoing revisions to ISS staging, while better reflecting current evidence and standard of care.

Although out of scope for this comment opportunity, ASH believes it is important to ensure that staging is not interpreted as a prerequisite for AuSCT. We would welcome the opportunity to discuss alternative criteria that could support the future removal of staging language in the NCD.

Once again, the Society thanks the Agency for proposing to revise and expand coverage in this policy beyond an outdated standard and for CMS's consideration of this request above. ASH remains available as a resource to CMS and would be happy to identify subject matter experts as needed. Should CMS have any questions or wish to further discuss the suggested clarification, please contact Carina Smith, Manager for Health Care access Policy (casmith@hematology.org).